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5. Question to Colleagues: Do you count mitotic figures in melanomas measuring 1 mm or less in thickness?

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The question

The following letter was sent via email to numerous colleagues:

Dear Colleague,

For the next issue of the Journal *Dermatopathology: Practical & Conceptual* we would like to learn your opinion about the following matter:

Recently a new melanoma classification has been suggested. [1] The authors state that *"primary tumor mitotic rate is now a required element for the seventh edition melanoma staging system."*Mitotic rate is used in this classification to determine T1b melanomas.

1. Do you count mitotic figures in melanomas measuring 1 mm or less in thickness?

2. What is your opinion about mitotic rate being a prognostic factor in melanomas measuring 1 mm or less in thickness?

Your reply within the next month is greatly appreciated by

Almut Böer-Auer, M.D.

Editor-in Chief

Dermatopathology: Practical & Conceptual

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Here we present the answers as they were received (in alphabetical order of author's last name).

Reply by Masoud Asgari, M.D., New York, NY, USA

My answer for the first question is no. I have never counted and I will not because it is not precise. For your second question, I think counting mitotic figures has no place for predicting the outcome of melanomas measuring 1mm or less in thickness because it is more interpretive and less reproducible.

There is no good and well-accepted precision for counting mitosis in sections of tissue stained with H&E and there is no evidence to show mitotic index would be used as a sole factor to determine prognosis in thin melanoma. We already know that the presence of mitosis has not enough specificity and sensitivity for diagnosis of melanoma [1-4]; it also should not be used as a predictor for prognosis of thin melanomas.

A brief perspective review would help to understand the lack of unanimity in assessing histological parameters in prediction of melanoma's outcome among experts of JACC. In 2000, the member of AJCC suggested "melanoma thickness and ulceration, but not level of invasion, to be used in the T classification [5]; A year later "level of invasion" was included only in T1 category which encompasses those melanoma with I mm or less in thickness. [6] Three years later in 2004 the very same group proposed "melanoma thickness and ulceration are the dominant predictors of survival in patients with localized melanoma (Stages I and II); deeper level of invasion (i.e., IV and V) was independently associated with reduced

survival only in patients with thin or T1 melanomas." It is clear that they brought back "level of invasion" and put it in their cancer staging system for cutaneous melanoma but just emphasized on level IV and V of Clark as independent predictors. [7] In 2009, members of Melanoma Staging Committee of the AJCC (Byrd DR, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Sondak VK joined the group in this year) acted in a different way. They added mitotic rate (histologically defined by them as mitoses/mm (2)) and suggested to use it along with thickness and ulceration as the most dominant prognostic factors and recommended level of invasion being replaced by mitotic rate "as a primary criterion for defining T1b melanomas." [8] In other words, they found out that "mitotic rate" works better as a prognostic factor than "level of invasion" as defined first by Wallace Clark in 1969. I believe both fail for different reasons and should not replace one for another.

Although melanoma prognosis depends on many variables and the influence of each in prognosis is unclear for us at the time of diagnosis, the vast majority of previous studies have shown that the most important factors in prognosis of melanoma are thickness and ulceration. [9-15] Mitotic rate in thin melanomas is currently being considered as another important prognostic factor. Although previous studies declared mitosis is neither accurate nor reproducible to predict outcome of melanoma, [16-19] newer ones are revealing high mitotic rate is associated with higher risk of lymph node involvement at the time of diagnosis and may have an independent impact in prognosis. [20-22]

Mitosis is a histopathologic feature that is pertinent to what we call "grade of a neoplasm." On the other hand, staging is related to local and distance extension and distribution of a neoplasm. As a general rule, staging is always more accurate than grading as a predictor for malignant neoplasms. Grading of a neoplasm (mitotic rate, pleomorphism and maturation) is rarely used alone for prognosis; rather it is used in combination with staging. However, there are exceptions, for example, everybody knows Gleason's grading system still remain as one of the most powerful prognostic predictors in prostatic cancer and still has major impact in prognosis and is comparable with the staging system in prediction of survival in patients with prostatic cancer. Another example is breast carcinoma in which grading system as staging system would have significant histologic outcome for patients who suffer from invasive ductal carcinoma.

Considering all, I believe mitosis has no major impact in prognosis of thin

melanoma, and if it would, it is not independent. Histologic parameters such as mitotic rate, growth and extension of melanoma into the dermis or subcutaneous fat, or upward into the epidermis (which would cause ulceration), penetration into the local and distance vessels, lymph node distribution and distance metastasis are interrelated factors and they should not be interpreted as independent predictors. This issue being more complicated when other variables such as host immunologic responses as well as genetic background are being in consideration. Still there are other parameters which have not been elucidated. They are not easily identified and not easy to take into account. There are several examples of thick melanomas with high mitotic rate and even with metastasis but with good patient's survival and conversely thin melanomas with ominous outcome. Until biology and natural course of melanoma have been understood completely, we are unable to find reasonable answer for this phenomenon. Of course, among all these factors, thickness of melanoma and ulceration have a good precision to assess histopathologically and intraobserver and interobserver agreement on them are much more reproducible between pathologists and dermatopathologists than counting of mitosis or estimation of "Clark's level of invasion."

In sum and in short, because mitosis is one histological element of grading systems, I do not use it as a sole prognostic factor in melanoma less than 1 mm in thickness. It is more interpretive and not very sensitive. "Clark level of invasion" is neither accurate nor reproducible than Breslow thickness for predicting of melanoma's prognosis.

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Reply by Larry Buckel, M.D., Greenwood, IN, USA

No to both!

Reply by Lorenzo Cerroni, M.D., Graz, Austria

1. I use the AJCC 2009 staging system, thus I check mitoses in thin melanomas.

2. We never checked that parameter before, thus I cannot answer the second question as personal experience is lacking; in the last 5 months I did not found cases with mitoses >1/mm2

Reply by Bernard Cribier, M.D., Strasbourg, France

1. We never count mitoses in such cases.

2. I cannot believe that the mitotic rate can reliably be established in thin melanomas and I am very surprised it is now considered as a prognostic factor.

Reply by Geoffrey J. Gottlieb, M.D., New York, NY, USA

1. NO. I never count mitotic figures, even in thick lesions.

2. My impression from what I know of the literature is that the # of mitoses has not been shown to be a reliable prognostic indicator. Many (?most) of the authors of the cited paper are not dermatopathologists and many are authors of papers which are statistically suspect.

Reply by Jane Grant-Kels, M.D., New Haven, CT, USA

1. Yes.

2. I think it is appropriate and will help in prognostication for thin melanomas.

Reply by Joan Guitart, M.D., Chicago, IL, USA

We count dermal mitosis on all invasive melanomas. In our small series of 43 thin metastasizing melanomas (Breslow's <1mm), only 8 cases had dermal mitosis (n/s). Extensive regression was found to be the only significant histological features between the metastasizing and non-metastasizing groups (Arch Dermatol 2002). But again this was a small cohort. Early nodular melanomas with nevoid features often have notable dermal mitotic activity and this is definitely a red flag. In my opinion, dermal mitosis in thin melanomas reflects tumorigenic phase and therefore is of great concern.

Reply by Markus Hantschke, M.D., Friedrichshafen, Germany

1. I do not count mitotic figures in melanomas measuring 1 mm or less in thickness on a general basis. Melanomas of this thickness surprisingly often show hardly any

mitotic figures and still can lead to metastases.

2. The emphasis of mitoses as a prognostic factor in melanomas raises a lot of questions. The scientific objectivity of this statement is not generally accepted. Only ulceration and tumor thickness have proven to be of significant prognostic meaning in major studies.

Counting mitotic figures per square mm in melanomas measuring less than 1 mm in tickness might indicate a false impression of scientific objectivity. Moreover, the potentially different meaning of mitoses at the junction, in the dermal part and at the basis is not appreciated.

Profound major studies should be recommended before including a factor in a new melanoma classification.

Reply by Mark A. Hurt, M.D., Maryland Heights, MO, USA

1. I do not count mitoses in melanomas, nor do I recognize any specific "type" of melanoma as such (1). I *do* recognize the fact that some melanomas contain melanocytes that harbor nuclei in various stages of mitosis. In some cases, the mitotic figures are abnormal; in other cases, many mitotic figures are identified. Mitoses, their number and quality, aid often in the *establishment* of the diagnosis of melanoma. A mitotic figure is, however, a criterion that I use in conjunction with other criteria, both structural and cytological, to aid in establishing a diagnosis. I neither count them nor do I provide an "index."

2. The issue is not the *number* of mitoses in a proliferation of melanocytes but whether the *presence* of them aids in *establishing* the diagnosis of melanoma. A prognosis is a complicated evaluation based on a large number of patients with a given diagnosis. My role as a diagnostician is to establish the diagnosis as such, i.e., whether a lesion *is* melanoma, not whether the patient will or will not *die* from melanoma (2). That is a question of which no one knows the answer for a given patient. As for the mitotic index in this context, I regard it the same way I regard the Breslow thickness and the Clark level. For an individual patient, they have no meaning. They have relevance only when evaluating thousands of patients, which is the purview of epidemiologists and oncologists, not pathologists and

dermatopathologists.

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Reply by Doina Ivan, M.D., Houston, TX, USA

Yes, we do count the mitotic figures/square mm (approximately 4 and 1/2 high power fields) for every case of invasive melanoma. If the dermal component is very small, we usually mention this (I guess, the presence or absence of mitotic figures in dermal melanocytes is somewhat not so statistically significant when there are only few dermal melanocytes to be evaluated). Moreover, in our institution if we report vertical growth phase based on presence of mitoses in dermal melanocytes (not based on a larger dermal melanocytic nest), this warrants a sentinel lymph node procedure. As a note, 2 of the co-authors of the new AJCC melanoma classification that you mentioned are melanoma surgeons in our institution and many cases that we have examined have been used for this study.

Reply by Friederike Kauer, M.D., Berlin, Germany

1. Not yet, but I will try and start from now on. For now we can do it only with HE, no immuno.

2. In very thin melanomas I rarely see a mitosis, even in 1mm thickness I don't see that much. But maybe I haven't paid enough attention. But I am a little bit surprised that it is now an important prognostic factor. I am very unsure about the method how to count correctly (+HE / immuno) and there is no advice for which number of mitosis a SNB should be done in melanomas less than 1mm. I suppose that the

counting can be interindividually very different and so I doubt a little bit if it is really a reliable prognostic factor.

Reply by Werner Kempf, M.D., Zurich, Switzerland

We count mitoses in all melanomas <1mm, but in our experience the number is low—with the exception of nevoid melanoma. We consider thin melanomas with mitotic activity as a somewhat more aggressive, although we do not have statistic data to confirm this hypothesis.

Reply by Helmut Kerl, M.D., Graz, Austria

Presence of mitoses and mitoses near the base is an important criterion in the distinction of melanoma from benign melanocytic nevi.

1. I do not count mitotic figures in melanomas measuring 1 mm or less in thickness.

2. There is not enough experience about the role of mitotic figures as a prognostic factor in thin melanomas.

Reply by Harald Kittler, M.D., Vienna, Austria

1. The answer to your first question is yes but I do not report the Clark level anymore.

2. I rely on the validity of the statistical analysis of Balch and coworkers. It is based on a significant number of patients and cannot be ignored. However, I predict that in the future we will see additional modifications based on mutational status and chromosomal aberrations. Microstaging will become more and more sophisticated and expensive and will be restricted to specialized centers. The major question is if this is what we want but this would require a different discussion.

Reply by Heinz Kutzner, M.D., Friedrichshafen, Germany

1. Yes, I do (following the great Galileo Galilei who supposedly asked all scientists "to measure whatever can be measured." If he had been an dermatopathologist, I am sure, he would have used the phrase "count everything").

In fact, I have been counting mitoses in malignant melanomas for more than 10 years, using various immunohistochemical approaches which facilitate the endeavor, i.e., antibodies against MPM-2, phospho Histone H3 serine 28, and phospho Histone H3 serine 10 (the latter being the best one of the trio). Counting mitoses in H&E stained slides of melanocytic lesions should be discouraged (sic!) as it is a very subjective proceduce, and very imprecise (just the opposite of what Galileo had in mind). A paper by Glatz et al (in print) in the American Journal of Dermatopathology shows clearly that discrepancies between mitotic counts in H&E stained and in immunostained sections, respectively, are appalling, and in scientific terms "intolerable," with H&E mitotic counting doing very poorly while immuno-counting produces much higher mitotic yields (mostly due to the optimal signal-to-noise ratio: in immunostains red mitotic dots stand out against a pale blue background. This type of counting is fast and precise, in fact, this is the method of choice). Just as an aside, mitotic counting should not be restricted to melanomas but also should be performed in unusual nevi and, needless to add, in Spitz nevi, deep penetrating nevi and others.

2. The number of mitoses as well as the location of the mitoses ("deep mitoses in spitzoid melanocytic lesions") are important for diagnosis of melanocytic lesions. As we all know, there are textbooks which propagate dogmas such as "more than 2 mitoses in a cellular blue nevus indicate ....." They may be right. So, mitoses are important. No question about it! But whether they are important indicators of prognosis, is a completely different story. We all have seen cases replete with mitoses, and a bland follow-up. And quite a few of the metastasizing melanomas turned out to show very few or "less than one or two" mitoses per any number of high power fields. However, these anecdotal ages are over (so is the enigmatic measure of the "high power field"). I believe strongly that we can no longer rely on anecdotal reports or gut feelings. Detailed studies (using large cohorts and adjunctive modern molecular techniques) are needed to solve the riddle of mitoses and prognosis. At the moment, hard data are rather scant (especially in regard to

the thin melanomas), and most of our cherished rules may be totally false! Notwithstanding all these limitations, it is my opinion that mitoses in thin melanomas may play only a secondary role in the prognosis game. We all know the phenomenon of oncogene induced senescence: there may be a "storm of mitoses" in a melanocytic lesion followed by "eternal sleep" of that monster. It may be quite similar in the thin melanomas—or not. Let's not forget, a histologic slide is like a single frame from a 90 minute film. It cannot tell the whole story! Admittedly, all of this may be wrong. Therefore, at the moment, I am very cautious and urge everybody to rely on multiple parameters, mitosis being one of them.

Reply by Rossitza Lazova, M.D., New Haven, CT, USA

We count and report mitotic figures in all melanomas regardless of their thickness. We have not studied and compared cases to see whether the number of mitotic figures correlates with prognosis.

Reply by Philip E. LeBoit, M.D., San Francisco, CA, USA

Because our practice is affiliated with a university medical center with a melanoma clinic, whose clinicians demand AJCC classification of melanoma, we do report mitotic rate and AJCC staging. However, I have some concerns that mitotic rate is an epiphenomenon.

1. Breslow initially tried to measure tumor volume, and then later decided that this was impractical and that thickness was a practical substitute for volume. Perhaps mitotic figures are difficult to find in thin melanomas with low tumor volume, and easier to find in melanomas of comparable thickness, but lower tumor volume.

2. Some of the thin "melanomas" without dermal mitoses may not be melanomas at all, but Spitz or dysplastic nevi.

I think this topic needs further study, including inter-observer comparison and testing to see if the mitotic rate changes from section to section.

Reply by John Maize, Jr., M.D., Charleston, SC, USA

We started counting mitoses in melanomas beginning on Jan 1st when the new guidelines took effect. We do have some dermatologic surgeons who began demanding it though I think most dermatologists are not yet aware of the change in the guidelines. The dataset regarding mitoses reported in the AJCC cancer staging manual seems to indicate a small but statistically significant decreased survival rate for patients with detectable mitotic activity even in melanomas.

Reply by Cesare Massone, M.D., Graz, Austria

1. Yes, I do. I apply the new classification system.

2. I think it could be a more reliable prognostic parameter than Clark level but mainly it can help in better staging and stratifying melanoma patients. I think the most relevant consequence is that there is a new subset of patients with tumor thickness <1mm that deserve sentinel node biopsy: this will help in diagnosing more patients with sentinel node metastasis and will change therapeutic approach.

Reply by Timothy McCalmont, M.D., San Francisco, CA, USA

1. I do, in the situation in which there is sufficient surface area (1 square mm or more) of tumor for a proper calculation to be made. As you know, for many melanomas of less than 1 mm in thickness, a calculation cannot be accurately made because of a lack of sufficient surface area.

2. I'm open-minded about the issue, provided the calculations underlying any data have been accurately made. (I haven't yet carefully studied the available data.)

Reply by Francois Milette, M.D., Longueuil, QC, Canada

1. This is the format in which I report infiltrating melanomas:

- Malignant melanoma, the histopathological characteristics of which are as follows:

- Anatomical site:

- Thickness (Breslow): ___ mm

- Mitotic activity: ___ mitoses/mm2

- Tumoral regression: Absent/Present

- Surface ulceration: Absent/Present

- Invasion:

- Vascular: Absent/Present

- Neural: Absent/Present

- «satellite nodules» (metastasis): Absent/Present

- Associated benign lesion: Absent/Present.

- If present, type:

- Surgical excision: Complete/Incomplete

I report mitotic activity for all melanomas except in situ melanoma. My measurement of this index is an average of 5 to 10 high power fields (HPF) when possible and is expressed in mitoses/mm2. If it is not possible to obtain at least 5 HPF then mitosis are reported either as "< 1 mitosis/mm2" if no mitosis is seen, or > 1 mitoses/mm2 if one or more mitosis is/are identified. This is all COMPLETELY ARBITRARY but I think that in a 0.1 mm2, thin melanoma (so-called "micro-infiltrating"), if one mitosis is observed, it would be absurd to

extrapolate an index of 10 mitosis/mm2? But then, how many fields are needed? I require 5, should I require 10, or more? Or less? On the other hand, are only the most "active" fields to be reported? Or the least active? Or is it necessary to calculate a mean mitotic activity for all fields? And if one decides not to measure mitotic activity in thin melanoma because of lack of reliability, what will be the minimal conditions of "measurability"?

How futile these questions are!

Among the characteristics that I continue to report, mitotic activity is certainly the one (together perhaps with surface ulceration) that appears to me the least reliable. A major source of doubt is that when cases I have diagnosed are reviewed by colleagues, our measurements most often differ. The reverse is also true: when I review cases diagnosed by colleagues, our measurements again differ. In short these measurements may be precise; they are not exact!

The more I reflect about this question, the more I think it is very possible that the result of the present survey will bring the slight upsurge of will I still need to abandon reporting mitotic index!

2. I give no more credit to mitotic index than to any other "prognostic factors" because I am convinced that it is far beyond our competence to predict the fate of an individual patient with any degree of precision higher than that implied by the diagnostic itself. In any way, the ultimate result of any prognostication for an individual patient can be summarized thus: either the conclusion is "It should go well but it might go bad" or "It should go bad but it might go well." No great achievement in my view!

Why then do I continue reporting the characteristics enumerated earlier? This is a good question indeed!

I turned to my colleagues clinicians to help me answer it beyond the simple argument of inertia. What came out from my discussion with them is that their therapeutic decisions are taken essentially on the basis of: (1) whether a melanoma is in situ or infiltrating; (2) the thickness of the lesion and (3) the presence or absence of metastasis. The other "prognostic factors" are used very loosely if at all! Moreover it was stressed by clinicians that, since there is no tool to integrate the multiple figures of purported prognostic significance, the practical utility of any

collection of them is limited. Too much is no better than not enough!

My conclusions from all this are:

1. It is important to state whether a melanoma is in situ or infiltrating. This of course is an evidence!!!

2. If in situ, the only thing that needs to be added is whether the excision is complete or not. This, of course must also be specified for infiltrating melanomas.

3. If infiltrating, the Breslow index is needed because it is on it that many therapeutic decisions are made. As required by the clinician (not the patient!) it necessarily is of clinical utility. If one omits the Breslow index from one's report, one will be disturbed very often by the clinicians!!!

4. Some characteristics have been shown in the literature to have biological significance similar to that of metastases (vascular invasion, satellite nodules and regression) and, for this reason, I report these characteristics which are not "prognostic" but "diagnostic."

Concerning mitotic index and the presence/absence of surface ulceration, their significance is far weaker. Just try to "forget" these characteristics in a report and see what happen!!! I am certain that, no decision being made on their basis, your forgetting will go unnoticed!!! And if a clinician were to justify a specific therapeutic decision using the mitotic index or the presence/absence of surface ulceration, I would seriously question his seriousness!!!

5. The presence of an associated benign lesion is of some interest histopathologically and biologically and may be retained.

Of course if panels of experts decide to modulate therapy on the basis of mitotic index, then mitotic index will become mandatory but until then, the pertinence of mitotic index remains essentially statistic and therefore, in my opinion, useful in a research context exclusively.

If the spirit that inspires the multiplication of prognostic factor mandatory in pathology reports is to be adopted, I suggest that chromatin heterogeneity, diameter

of nucleoli, AgNOR, and any other characteristic once studied in the literature, also become mandatory. Including everything once and for all would at least spare us the burden of studying a new "classification" each year!!!

Reply by Sabine Oeschger, M.D., Marburg, Germany

I do not have enough experience with melanoma especially clinically. The rate of mitoses does have a meaning in regard to the aggressiveness of some tumors such as breast carcinoma and sarcomas, but this is relevant for the grading of theses tumors and not for the TNM classification, at least up to now. However, classifications are changed continuously.

Reply by Bruno Paredes, M.D., Friedrichshafen, Germany

1. We do not (yet) count the number of mitotic figures. Hereby one should also know the number of mitotic figures in melanocytic nevi; this as a starting point for the malignant analogue.

2. Another important question: What is the level of evidence of the TNM-system? The never ending corrections and adaptations seem to militate against good evidence. Does this system work well? It is only a question of time that counting mitoses in thick melanomas will also be required etc. Are there evidence bases studies about the numbers of mitoses in melanomas less than 1 mm in thickness? Why collect this data? Who has an honest interest in knowing the number of mitotic figures? The number of exceptions is too high in melanomas: Thick melanomas with few mitoses, melanoma metastasis devoid of mitoses . . . Where is the standard? Only with a logical and comprehensible explanation I would count the number of mitotic figures without revulsion. Moreover, in melanomas below 0,5mm in thickness, the number of mitoses is almost always below 1 square millimeter.

Reply by Victor Prieto, M.D., Houston, TX, USA

We have been counting mitotic figures in all invasive melanomas. According to our experience, mitotic counts are only secondary to Breslow thickness when determining melanoma prognosis.

Reply by Christian Rose, M.D., Lübeck, Germany

1. Not until now, but when the new version of the AJCC melanoma classification becomes valid I will be required to do it.

2. Up to now, I have not studied in detail the published data about this issue. If the mitotic rate is a prognostic factor, then it is worth counting mitotic figures.

As the general prognosis of thin melanomas is superb, I would suspect that the prognostic statement of the mitotic rate would better fit for thicker melanomas. This was already shown in the 70s by a thorough study by Schmoeckel. [1]

It would be important to give detailed information to the histopathologists, how these mitoses are counted. At least for me, it can be difficult to recognize mitotic figures clearly. Pyknotic nuclei can look very similar. What should be done with these nuclei? How thick should the tissue section be cut? Can immunohistochemistry improve the detection rate?

The differential diagnosis of thin melanomas is difficult and und requires profound experience including knowledge about clinical dermatology. According to A.B. Ackerman, the main task should be to render a correct diagnosis, which is reproducible and reliable, instead of speculating about the prognosis. [2]

At the end of my day, sitting at my microscope weighing up criteria on a given small melanocytic lesion from the back of a young woman, I asked myself how Bernie Ackerman would answer these two questions. I can hear him clearly.

References

1. Schmoeckel C, Braun-Falco O. Prognostic Index in malignant melanoma. Arch

Dermatol 1978;114: 871-873.

2. Ackerman AB. Histopathologists stick to your last: your job is diagnosis, not prognosis! Dermatopathol: Prac Conc 2000, 6: 315-319.

Reply by Omar P. Sangueza, M.D., Winston-Salem, NC, USA

1. Yes we do, because our surgeons request this number in all the reports. I do this to avoid telephone calls.

2. I believe that is a waste of time and does not help with prognosis.

Reply by Christopher R. Shea, M.D., Chicago, IL, USA

1. We measure dermal mitotic figures for invasive melanoma of all thicknesses.

2. Mitotic rate does indeed seem to be a crucial, negative prognostic factor for melanoma.

Reply by Wolfgang Weyers, M.D., Freiburg, Germany

In thick melanomas, mitotic figures obviously may play a role in determining diagnosis. If a melanoma has very many mitotic figures, that seems to be a poor prognostic sign. In thin melanomas, however, mitotic figures are rare. One hardly ever sees one. This implies that any count is highly arbitrary. If we see one mitotic figure in many step sections, we might as well see none. Moreover, mitotic figures are not always easy to distinguish from pyknotic nuclei. If there are many mitotic figures, one can dismiss the one in which one is not sure, but if that single one makes a difference, this cannot be done. Another problem is that the new guidelines of the AJCC do not specify whether only mitotic figures in the dermis or also those in the epidermis should be counted. Obviously, the count will be very different depending on which approach is taken, and when mitotic figures in the epidermis are included, they may be confused with mitotic figures in keratocytes,

further diminishing the reliability of any count.

It has long been said that mitotic figures are very rare in melanocytic nevi (other than Spitz's nevi). Recent studies have shown that they are not so uncommon if one looks for them thoroughly. If one starts to look thoroughly for mitotic figures in thin melanomas, one probably will find some more often than expected. The method to determine the mitotic rate recommended by the AJCC is the "hot spot method." This means that one starts to count at the spot where mitotic figures are most frequent and then counts the number of mitotic figures in the immediate vicinity until one square millimeter is covered. Hence, if one applies the "hot spot method" and sees one mitotic figure in 1,000 serial sections, the mitotic rate is at least one. Not every pathologist, however, will look for mitotic figures in 1,000 serial sections. For all those reasons, the interobserver reliability in the count of mitotic figure must be highly variable.

As a consequence, the data on which the recommendations of the new AJCC staging system concerning distinction between stage T1a and T1b (the latter harboring one or more mitotic figures per square millimeter) are based are questionable in the extreme. Moreover, the consequences of distinction between stages T1a and T1b are negligible. The only difference is the recommendation by the AJCC that in selected cases of patients with stage T1b sentinel lymph node biopsy should be considered, which, after all, is also nothing but a staging procedure that does not offer a therapeutic advantage, having shown not to enhance survival rate. In sum, the recommendation to count mitotic figures in thin melanomas is based on invalid data and of no consequence. Why, then, should one count mitotic figures?

We currently do not count mitotic figures in thin melanomas. However, because of the mania produced by the new staging system, questions concerning the number of mitotic figures are starting to abound, even in the case of specimens removed by curettage, and, therefore, we may be forced to name a number. Instead of searching thoroughly through 1,000 sections, however, we will give a rough estimate, as most pathologists will. How much effort do you want to put in the establishment of a finding that has no validity? And if our data enter into a multi-center study, they will be no worse than those used for the regression analysis on which the new AJCC staging system is based.

Reply by Bernhard Zelger, M.D., Innsbruck, Austria

I have always taken care for the presence of mitoses in melanomas and reported those findings in my reports. Mitoses frequently are regarded as a "worrisome" feature in melanocytic lesions and, indeed, in some cases one or more deep or even atypical mitosis/mitoses may be helpful for the diagnosis of melanoma. Yet, in my experience their value is overestimated. Mitoses are only one of many features, which by circumstantial evidence allow the diagnosis of melanoma. One or even more mitoses per se, independent if superficial or deep, are neither a criterion of malignancy (in contrast, in my experience melanocytic nevi, type Spitz, have much more and more frequently mitoses than melanomas thinner than 1.0 mm) nor are mitoses in my experience a prognostic factor in the course of disease.